

Voltage gated potassium channel antibodies positive autoimmune encephalopathy in a child: A case report and literature review of an under-recognized condition

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Abstract

Autoimmune limbic encephalitis (LE) associated with voltage gated potassium channel antibodies (VGKC-Abs) in children is more common than previously thought and is not always paraneoplastic. Non-neoplastic, autoimmune LE associated with VGKC-Abs has been described recently. However, only few case reports in children as the disease is predominantly described in the adult population. It is likely that this type of autoimmune encephalitis is currently under-diagnosed and hence, under-treated, especially in children. We present a 13-year-old previously fit and healthy African girl diagnosed with LE and we reviewed the literature for its current management.

Key Words

Limbic encephalitis, paraneoplastic, voltage gated potassium channel antibodies

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Introduction

Limbic encephalitis (LE) is a sub-acute syndrome presenting with confusion, episodic memory impairment, hallucinations, sleep disturbances, seizures and abnormal signal change in the limbic structures (medial temporal lobe or hippocampus) on magnetic resonance imaging (MRI). Though traditionally considered to be paraneoplastic in origin, many specific non-paraneoplastic auto-antibodies have also been identified in the recent years.^[1]

Voltage gated potassium channels (VGKC) are a family of voltage-gated shaker-like potassium channels, which are membrane proteins, responsible for controlling the cell membrane potential. Non-neoplastic autoimmune LE, associated with VGKC antibodies (VGKC-Abs) has been recently described.^[2] Recent investigations have shown that most of the antibodies thought previously to be directed towards the VGKCs, are, in fact, binding to other proteins

that could be identified in complexes with VGKCs in extracts of mammalian cortical neuronal membranes. The antibodies bind mainly to proteins such as leucine-rich glioma inactivated 1 (LG1) and contactin associated protein 2 (CASPR2) or, less frequently, Contactin-2, all of which are components of VGKC complexes.^[3] However, very few cases are reported in paediatric population. We describe a 13-year-old girl presented with confusion and seizures and had high titers of VGKC-Abs. Response to immunotherapy was very good, and she made near complete recovery.

Case Report

A 13-year-old, right handed, previously fit and healthy girl presented with a short history of generalised headaches and confusion. She had "flu-like" symptoms 4 weeks ago followed by complete recovery. There was no history of fever, drug ingestion, head injury, rash, tick bite or travel outside the country within last 6 months. Parents were non-consanguineous, Afro-Caribbean origin, and her father died at the age of 55 years from a "possible stroke."

On admission, Glasgow Coma Scale was 13/15 and she was aggressive and disorientated. She was afebrile with normal blood pressure and heart rate. There were no focal neurological signs, and general examination was unremarkable. Soon after admission she developed left focal motor seizures with secondary generalization, requiring intensive care treatment

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for the next 3 weeks. Seizures were difficult to control, and she had repeated episodes of status epilepticus, requiring multiple anticonvulsants. Repeated electroencephalogram (EEG) showed diffuse generalised slowing with no epileptiform discharges.

Initial blood investigations were unremarkable, including full blood count and peripheral smear, baseline electrolytes, renal, liver and bone profile, haemoglobin electrophoresis, peripheral blood film for malarial parasites, investigations for tuberculosis, antibodies for *Borrelia burgdorferi* and human immunodeficiency virus. Highest C-reactive protein was 85 in the 1st week. Initial cerebrospinal fluid (CSF) was reactive with 34 white cells/mm³ (80% lymphocytes), normal glucose (more than 50% of blood glucose) and protein. Polymerase chain reaction (PCR) for Herpes, Enterovirus, Cytomegalovirus, Human herpes virus 6 was negative along with urine for toxicology. Blood, urine and CSF cultures were sterile. First MRI brain [Figure 1] showed thickening of right temporal lobe gyrus, extending on to parietal lobe, with increased T2 signal within the cortex. There was associated restricted diffusion on diffusion-weighted imaging (DWI) [Figure 2]. She was treated for 2 weeks of third-generation antibiotics and acyclovir for probable encephalitis.

Post-intensive care she remained confused, disorientated and had recurrent episodes of aggression and rage. She became mute and developed visual hallucinations. Sleep cycle was completely disrupted, and she was emotionally labile. Seizures were difficult to control initially but responded to a combination of Phenytoin and Levetiracetam. Repeat CSF examination was clear with normal biochemistry. PCR for Herpes and other viruses were negative.

Serum VGKC-Abs were positive with titers of 1088 pM (normal < 100 pM). Further radiological investigations for possible underlying malignancy were negative. Treatment with high a dose oral prednisolone (60 mg) once daily for first 2 weeks followed by 4 weeks of weaning doses. The latency period from admission to immunotherapy was 3 weeks. There was slow but significant improvement in her symptoms following immunotherapy. The repeat serum VGKC-Abs titers

after immunotherapy were negative, consistent with her clinical improvement. The neuropsychological evaluation before and after the immunotherapy suggested significant improvement in her cognition and behavior.

Repeat MRI brain done after the treatment showed a reduction in the gyral thickening with improved grey-white matter differentiation and normal DWI. She received intense neurorehabilitation based at hospital and community following discharge. She has restarted in mainstream school after 6 months and has made near complete recovery.

Discussion

Autoantibodies and its role in various neuromuscular disorders have been recognised for more than 40 years since the breakthrough finding of antibodies to the acetylcholine receptor in myasthenia gravis. The advancement of neuro immunology over the past 10 years has helped the discovery of immune-mediated diseases, which are associated with antibodies to cell-surface proteins expressed in neurons, and the fact that these patients can improve with immunotherapies. Few patients with Autoantibodies have tumours like ovarian Teratoma, thymoma, or small-cell lung cancer, but most do not have detectable tumours.^[3] The disorders associated with these antibodies have previously been termed autoimmune channelopathies, even though some of the antigens are not the channels themselves but proteins that are complexed with them on the plasma membrane of neurons, their axons, dendritic spines, or nerve terminals. Several antibodies have been identified so for using indirect immunohistochemistry (immunofluorescence)- N-methyl D-aspartate (NMDA) receptors antibodies (NMDAR Abs), VGKC complex antibodies (VGKC-Abs), antibodies to alpha-amino-3-hydroxy-5-methylisoxazole-4- propionic acid (AMPA) receptors (AMPA), Gamma-aminobutyric acid (GABA) type B receptors (GABABRs), Glutamic acid decarboxylase antibodies (GAD Abs), Glycine receptor antibodies. Non-paraneoplastic, autoimmune LE associated with VGKC-Abs is a very rare condition with variable prognosis and only few children have been described in the English literature. First described by Buckley *et al.* in 2001,

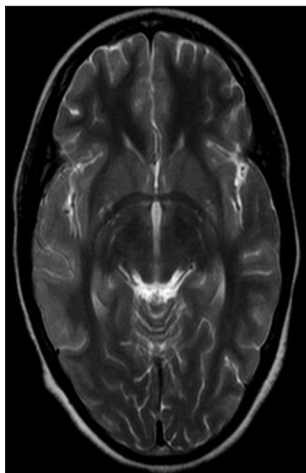


Figure 1: Axial T2 weighted imaging showing thickening of right temporal lobe gyrus with increased signal in the cortex

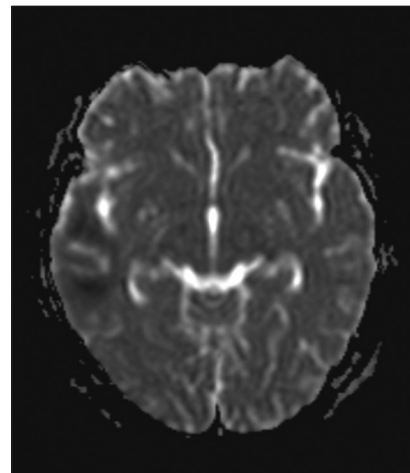


Figure 2: Diffusion-weighted imaging highlighting restricted diffusion in the right temporal region, corresponding to Figure 1

it has now been reported world-wide.^[4] High titres (>400 pmol/L; normal values < 100 pmol/L) were detected in serum samples of patients in a retrospective UK study at the rate of about 1-2 per million per year.^[5]

Patients with LE and VGKC complex Abs present with acute to subacute onset memory loss, confusion, temporal lobe seizures (typically faciobrachial dystonic type), agitation, sleep difficulties and other psychiatric features evolving over several days to weeks [Table 1]. Sometimes, they may have a preceding history of systemic infection. Most patients are older than 50 years with male predominance. Currently, the condition is under recognized in children all over the world due to various reasons, which included reduced awareness of the condition, so the ideal opportunity to treat early with immunotherapy is missed.

Viral encephalitis, toxin or drug-induced encephalopathies should be considered in the differential diagnosis. Low sodium concentrations in plasma (between 115 mmol/L and 130 mmol/L) are noted in 60% of the patients due to hypothalamus involvement.^[3]

Concentrations of serum VGKC complex antibodies are typically high (>400 pmol/L) in patients with LE, often higher than 1000 pmol/L, but lower values (100-400 pmol/L) can be detected especially in children, and in those sampled later in the disease when some recovery has occurred, or in patients who improve.

Spontaneously.^[6,7] Paraneoplastic forms of LE due to VGKC-Abs are rare, but it must be excluded with serology for onconeural antibodies and appropriate body imaging.

Pathogenicity of VGKC-Abs has been demonstrated by animal passive-transfer experiments and *in vitro* suppression of potassium currents. Immune-staining of molecular layer of the dentate gyrus have highlighted that hippocampus is predominantly affected by these antibodies.^[2,3] The therapeutic

benefit of immunomodulation is also consistent with a humoral immune pathogenesis. CSF analysis is usually normal, but some patients have pleocytosis and elevated proteins with oligoclonal bands suggesting a lack of significant intrathecal synthesis.

MRI findings of high signal in T2 or fluid-attenuated inversion recovery in the mesial temporal lobes, either unilaterally or bilaterally is common, but up to 45% of patients with LE with VGKC complex antibodies can have normal MRI.^[8] Positron emission tomography can be more sensitive in detecting hippocampal dysfunction than MRI, and can show altered metabolism (hypermetabolism early in the disease; hypometabolism at late stages) in the limbic areas.^[9] EEG usually shows interictal foci of epileptiform activity or slowing over antero-temporal or mid-temporal (sometimes also frontal) regions and ictal activity in the same areas.^[10]

Reid *et al.* described seven adults with VGKC-Abs associated LE.^[11] Diagnosis was made 3 months after the disease onset, and all patients had generalised or complex partial seizures. Two patients developed psychosis, four had anterograde memory loss, and two had global cognitive impairment. VGKC-Abs levels ranged from 857 to 3331 pM (mean 2146 pM) and all patients had abnormal MRI. Five had changes in the hippocampus and medial temporal lobe. All patients received immuno-modulatory therapy, and five patients made a good recovery in parallel with reduced VGKC-Abs titers.

Haberlandt *et al.* described clinical profile and outcome of ten children with autoimmune LE from across the Europe.^[7] This is a recent study from 12 institutions; 10 patients were identified as having LE according to their clinical presentation and radiological evidence of mediotemporal lobe inflammation. Four children had low titers of VGKC-Abs (143-310 pmol/l) and two of these associated with high titers of antibodies to Glutamic acid decarboxylase (GAD). All four had confusion, memory

Table 1: Comparison of various features following voltage gated potassium channel antibodies and NMDAR-Abs limbic encephalitis

	VGKC Abs	NMDAR-Abs
Age	Common in adults and older age (>50 years) reported in children	Usually <50 years and documented well with paediatric age
Male female ratio	2:1	Common in females (1:3)
Clinical features	Predominantly limbic encephalitis with amnesia, seizures, psychiatric disturbance, sleep difficulties, faciobrachial dystonic seizures refractory to normal anticonvulsants, hyponatremia (in 60% due to hypothalamus involvement and SIADH)	Multistage cortico-subcortical encephalopathy including psychiatric manifestations, seizures, disorientation; usually progress after 1-3 weeks to dyskinesias and other movement disorder (choreoathetoid), mutism, reduction in consciousness and hypoventilation, dysautonomia
Antibodies and target structure	VGKC-complex-associated LGI1 Abs more frequent than CASPR2 Abs hippocampus	NMDAR (mainly NR1 subunit, hippocampus, subcortically in the brainstem, the basal ganglia, or the cerebellum)
Tumour association	Very rare (<10%-thymoma, small cell lung cancer)	Ovarian teratoma (20-50%)
MRI	Hippocampal high signal in 60%	Normal in most. Occasional non-specific high signal on medial temporal lobe
CSF analysis	Mostly normal	Early lymphocytic pleocytosis and later oligoclonal bands
Immunotherapy	Good response usually with steroids and/or IVIGs/plasma exchange	Slow response with various immunotherapies. May relapse following treatment

VGKC Abs=Voltage gated potassium channel antibodies, NMDAR=N-methyl D-aspartate receptors, MRI=Magnetic resonance imaging, CSF=Cerebrospinal fluid, CASPR2=Contactin associated protein 2; LGI1=Leucine-rich glioma inactivated 1, SIADH=Syndrome of inappropriate antidiuretic hormone secretion

impairment, and focal seizures. They were treated with steroids, and one child also had intravenous immunoglobulin (IVIG). All had further radiological investigation, but no tumors found. One child died, and three were left with neurological sequelae. The authors have suggested that LE with VGKC-Abs in adults usually has a favorable prognosis. This may be because the Abs were generally not looked for early during the children's illnesses and in turn missed opportunity for early immunotherapy. VGKC-Abs tends to show rapid fall after treatment, and it is suggested to repeat the antibody testing after a course of immunotherapy.

A 9-year-old girl has been described with VGKC-Abs associated LE and had subacute memory impairment and cognitive decline.^[12] EEG was abnormal and CSF was positive for oligoclonal bands. MRI showed bilateral, symmetrical, hyper intense lesions in insular cortex and hippocampus. VGKC-Abs were 127 pM and normalised after immuno-modulation, and she has made gradual recovery. Drug resistant Temporal lobe epilepsy with hippocampal sclerosis has also been described with LE associated with VGKC-Abs, in a 13-year-old girl.^[6] Treatment with steroids initiated after 2 years of initial presentation led to transient reduction of seizures.

Our patient had a rather acute presentation and atypical MRI findings. The diagnosis of LE was not suspected in the initial phase, as is often the case. High titers of VGKC-Abs and clinical response in parallel to the decline, following immunomodulation with steroids, suggest their likely pathogenicity. Seizures are often refractory and show a poor response to conventional antiepileptic drugs, but respond well to immunotherapies such as steroids, plasma exchange, and IVIG. Plasma sodium concentrations often normalize and VGKC-complex antibodies are usually undetectable within a few months in patients who are treated adequately. The antibodies will not reappear following careful weaning of steroids in most cases, and they seem to have a monophasic rather than chronic or relapsing remitting disease, but, in a small proportion of patients, the antibodies persist or reappear, and the patients improve slowly or relapse.^[3] Optimum treatment of VGKC-Abs associated LE has not been studied in prospective randomized studies. Wong *et al.*^[13] in an open-label prospective study of 9 patients described a combination of immuno-modulatory treatment in patients with VGKC-Abs associated LE. All patients had plasma exchange, immunoglobulin and methyprednisolone in the acute phase, followed by oral prednisolone. Immunological remission was achieved within 4 months along with improved imaging and cognition in the majority of patients. However, one patient died of septicemia.

It has been suggested that immunotherapy should be started as soon as LE is suspected. The ideal type of treatment has, however, not yet been established and may differ between the subtypes of autoimmune encephalitis. Many consider high-dose steroids or IVIG as viable first-line agents. Once the results of Abs diagnostics are available, these findings may contribute to further treatment decisions. Falls in titres of VGKC may serve as para clinical markers for the effect of immunotherapy. Patients with Abs to membranous antigens such as VGKC and NMDARs also benefit from plasma exchange.^[3]

Conclusion

Autoimmune LE associated with VGKC-Abs is more common than previously thought and is a potentially treatable condition. It is likely that this condition is currently under-diagnosed and hence, under-treated, especially in children. The potential reasons could be lack of awareness and its marked similarities to infectious encephalitis, in its symptoms and imaging. The clinical phenotype has expanded over the recent years and is likely to continue. Autoimmune aetiology must be aggressively looked for in a child with non-infectious, acute or sub-acute encephalitis.

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